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ARTICLE TYPE

Design, synthesis and antiproliferative activity of urocanic-chalcone hybrid derivatives

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Inspired by biologically active natural products, a hybrid analogue that combines the *N*-Me urocanic side chain of the sarcodictyin family of compounds with the chalcone motif has been proposed, synthesised and examined for antiproliferative activity in three cancer cell lines and one normal primary cell line. The analogues are all synthesised in one or two steps from commercially available materials and, of the compounds examined, the proposed hybrid analogue displays the most active and selective inhibition of cell proliferation in human colon cancer cell line HT29 (IC₅₀ 2.9 µM) and highly metastatic human breast carcinoma MDA-MB-231 (IC₅₀ 4.8 µM).

Introduction

Eleutherobin **1**^{1,2} and the structurally related sarcodictyin family of compounds **2**^{3,4} are natural products originally isolated from soft coral. They possess potent anti-tumour activity with a mechanism of action similar to paclitaxel (Taxol®) through the stabilisation of microtubules.⁵⁻⁸ They have attracted great interest as they display nanomolar cytotoxicity against a range of cancer cell lines including Taxol®-resistant cell lines^{5,9,10} (Fig. 1).

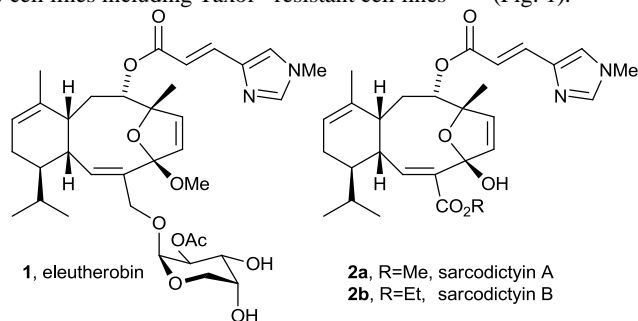


Fig. 1 Eleutherobin **1** and sarcodictyin A (**2a**) and B (**2b**)

Owing to their limited availability from corals, chemical synthesis is required to explore potential clinical application. The total syntheses of eleutherobin **1**¹¹⁻¹⁴ and sarcodictyins A (**2a**) and B (**2b**)^{8,15-17} have been reported. Extensive structure-activity relationships of the sarcodictyins were conducted and found that the α,β unsaturated urocanic ester side chain was vital for biological activity.^{8,17,18} Removal of this pharmacophore resulted in complete loss of cytotoxicity and even subtle substitutions of the imidazole ring were not tolerated and resulted in decreased activity.

Gennari has reported the synthesis of a variety of simplified eleutherobin analogues, using enantioselective allyltitanation reactions and ring closing metathesis (RCM) as key-steps,¹⁹⁻²³ culminating in the formal synthesis of eleutherobin.^{24,25} The

simplified analogues, exemplified by compounds **3** and **4**, retained potent microtubule-stabilising properties (ED₉₀ effective dose that induces 90% tubulin polymerisation) but exhibited reduced inhibition of tumour cell proliferation (IC₅₀ concentration inhibiting cell proliferation by 50%) (Fig. 2). It was suggested that this may be the result of hydrolytic cleavage of the *N*-methylurocanic ester due to a lack of substitution at C7, resulting in diminished activities, as the natural products are fully substituted at the equivalent position.²³ Although most studies show that the ester is essential to biological activity,^{8,17,18} Holmes reported simplified eleutherobin analogues **5** and **6** which displayed improved tubulin binding activities when the *N*-methylurocanic ester side chain was absent.²⁶

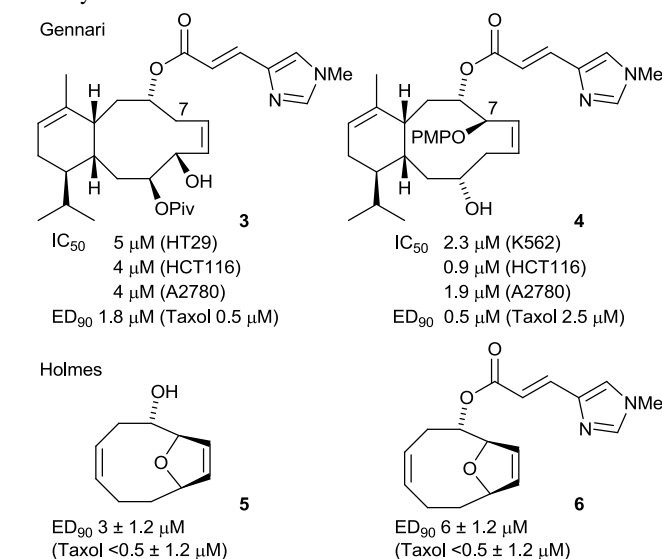


Fig. 2 Gennari^{21,23} and Holmes²⁶ simplified analogues.

Since the urocanic ester is required for potency in the natural products and can be susceptible to hydrolysis in simplified

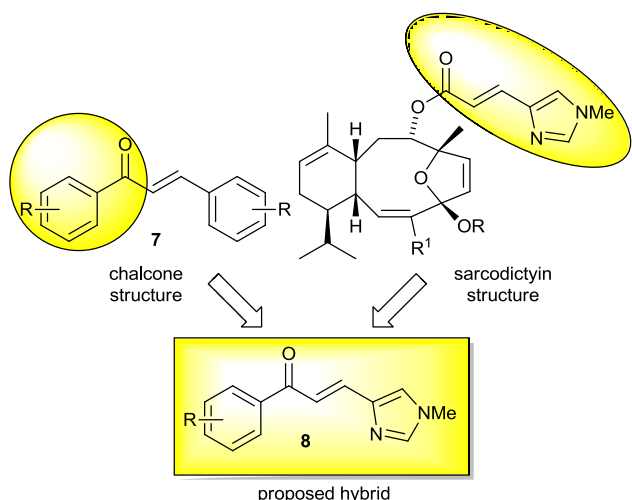


Fig. 3 Rationale for urocanic-chalcone hybrid.

analogues, we considered using ketone isosteres. Substituting the tricyclic core of the sarcodictyins with an aromatic group would generate compounds closely related to the structure of chalcones **7** that are biologically active compounds themselves.²⁷ We therefore proposed to investigate chalcone derivatives that feature the *N*-methylurocanic moiety, such as hybrid **8** shown in Fig. 3.

Despite the wealth of research in the area of chalcones and related compounds, very few examples have been reported which possess the framework of the proposed hybrid compound **8**. These include compound **8a** ($R = H$) generated as an intermediate in the synthesis of γ -lactam alkaloids.²⁸ The structurally similar compound **9** in which the enone is conformationally constrained has been previously reported and exhibits potent and selective inhibition of P₄₅₀ aromatase (P450 arom, CYP19), with possible therapeutic applications in various hormone-dependent cancers, such as breast, prostate and uterine (Fig. 4).²⁹⁻³³ Similar compounds have also been investigated as agonists of the α_{2B} and α_{2C} adrenergic receptors for the treatment of chronic pain.^{34,35}

The chalcone motif is a privileged structure present in an extensive range of biologically active molecules that display anti-inflammatory, anti-infective, anti-oxidative, anti-malarial and anti-cancer activities.^{27,36} Recent reports have shown chalcones having a trimethoxyphenyl group exhibit potent biological activities against various cancer cell lines, selected examples of which are shown by compounds **10**,³⁷ **11**³⁸ and **12**³⁹ in Fig. 4. The trimethoxyphenyl group is also present in a range of biologically active compounds such as colchicine **13**,⁴⁰ combretastatin A4 **14**⁴¹ and podophyllotoxin **15**,^{42,43} all of which also bind to tubulin but induce depolymerisation (Fig. 4).

Colchicine **13** and podophyllotoxin **15** display limited clinical potential due to severe toxicity; however, the phosphate prodrug of combretastatin (CA4P) is a promising lead compound under clinical evaluation.^{40,41,44} The success of combretastatin **14** demonstrates that structural complexity is not necessary for potent biological activity and that simple molecular scaffolds can provide new lead compounds. One emerging strategy in the development of new drugs involves combining key pharmacophores from existing natural products to generate novel chimeric compounds with improved biological properties.⁴⁵⁻⁴⁹

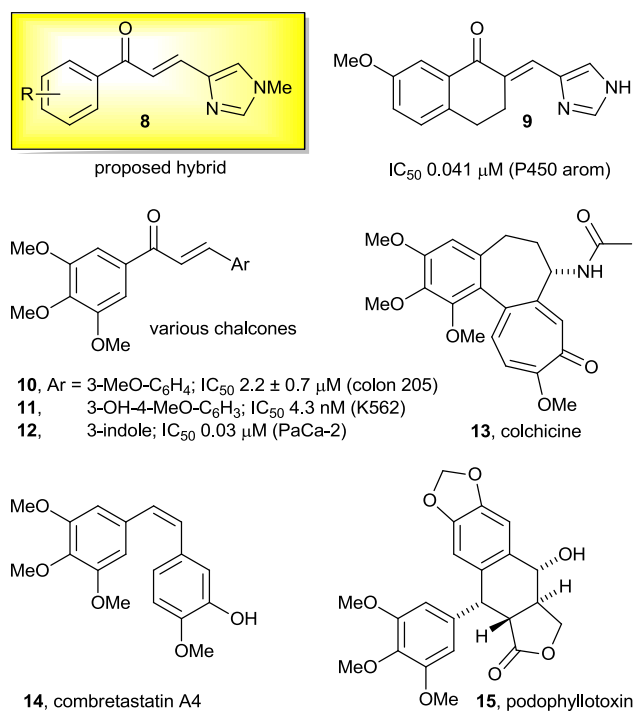


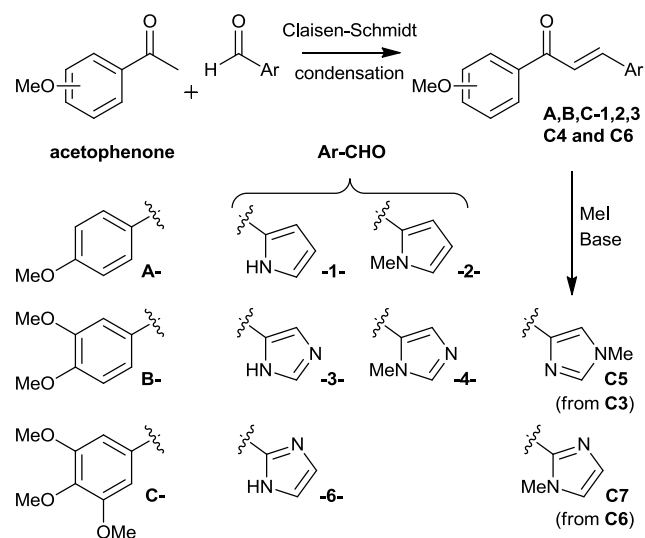
Fig. 4 Examples of biologically active arylmethylethers

Combining the pharmacophores of the trimethoxyaryl motif and the urocanic ester side chain, the synthesis and antiproliferative activity of various urocanic-chalcone hybrid derivatives is now described.

Results and discussion

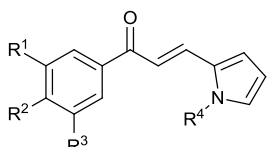
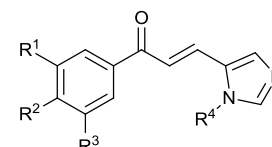
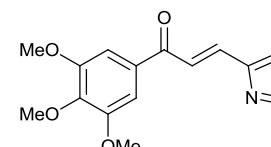
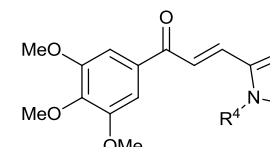
Chemical Synthesis

The chalcone hybrid derivatives were obtained by a Claisen-Schmidt condensation between the methoxy-substituted acetophenones **A**, **B** and/or **C** and the heteroarylcarboxaldehyde **1,2,3,4** and **6-CHO** (Scheme 1). *N*-Me imidazole derivatives **C5** and **C7** were obtained by methylation of the corresponding *N*-H imidazole, compounds **C3** and **C6** respectively.



Scheme 1 Synthesis of proposed urocanic-chalcone hybrid derivatives.

Table 1 Synthesis and inhibition of cell proliferation of various hybrid analogues

<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>A,B,C-1,2</p> </div> <div style="text-align: center;">  <p>A,B,C-3 and C4</p> </div> <div style="text-align: center;">  <p>C5</p> </div> <div style="text-align: center;">  <p>C-6,7</p> </div> </div>											
Entry	Compound	R ¹	R ²	R ³	R ⁴	Method ^a	Yield (%)	IC ₅₀ (μM) ^b			
								HT29	MDA-MB-231	LNCaP	FEK-4
1	A1	H	OMe	H	H	i	43	> 500	> 500	> 500	> 500
2	B1	OMe	OMe	H	H	i	53	86.0 ± 3.2	102.4 ± 3.7	104.6 ± 9.8	135.1 ± 37.2
3	C1	OMe	OMe	OMe	H	i	74	43.0 ± 8.0	49.9 ± 11.7	59.9 ± 9.2	156.1 ± 37.7
4	A2	H	OMe	H	Me	ii	63	61.8 ± 2.9	53.5 ± 5.7	75.5 ± 6.5	188.2 ± 91.8
5	B2	OMe	OMe	H	Me	ii	79	60.4 ± 13.1	42.8 ± 11.1	56.3 ± 12.4	161.7 ± 48.2
6	C2	OMe	OMe	OMe	Me	ii	83	12.5 ± 4.8	18.0 ± 7.7	69.5 ± 11.0	117.5 ± 24.6
7	A3	H	OMe	H	H	iii	53	23.6 ± 4.9	17.6 ± 4.7	33.5 ± 9.6	87.1 ± 14.1 ^c
8	B3	OMe	OMe	H	H	iii	74	37.9 ± 10.5	18.2 ± 2.1	46.2 ± 6.7	84.2 ± 19.0
9	C3	OMe	OMe	OMe	H	iii	74	19.5 ± 0.6	22.9 ± 3.7	48.1 ± 7.6	53.2 ± 7.4
10	C3-H ₂	OMe	OMe	OMe	H	iv	57	> 500	223.4 ± 20.6	367.7 ± 141.8	> 500 ^d
11	C4	OMe	OMe	OMe	Me	iii	54	15.9 ± 1.9	16.9 ± 1.5	30.6 ± 8.4	49.9 ± 1.9
12	C5	OMe	OMe	OMe	Me	v	36	2.9 ± 1.2	4.8 ± 2.3	48.4 ± 13.5	85.0 ± 25.9
13	C6	OMe	OMe	OMe	H	iii	38	5.0 ± 0.5	4.9 ± 0.9	17.1 ± 3.4	28.6 ± 10.7
14	C7	OMe	OMe	OMe	Me	vi	54	4.2 ± 0.6	4.9 ± 0.2	11.0 ± 3.6	17.5 ± 2.3
15 ^e	3	-	-	-	-	-	-	5 ^f	n.d	n.d	n.d
16 ^g	Doxorubicin	-	-	-	-	-	-	0.164 ^d	0.120 ^d	0.154 ^d	n.d

^a Methods (i) 1 equiv. LiOH.H₂O, (ii) NaOH, grinding, (iii) 2 equiv. BF₃.OEt₂, (iv) H₂, Pd/C, (v) NaH, MeI, DMF and (vi) Cs₂CO₃, MeI. ^b IC₅₀ is the concentration that inhibits 50% cell proliferation. Values are the mean from three independent experiments, except ^c two and ^d one experiment, with 5 quadruplicate readings in each. ^e Reference 21, ^f paclitaxel IC₅₀ < 5nM. ^g Doxorubicin was used as a positive control. n.d not determined.

LiOH.H₂O has been reported to catalyse the Claisen-Schmidt reaction of various aryl methyl ketones with heteroaryl aldehydes under mild conditions.⁵⁰ The reactions of 2-pyrrolicarboxaldehyde **1-CHO** with acetophenones **A**, **B** and **C** using 10 mol% of LiOH.H₂O, as described, were unsuccessful, although using 1 equivalent gave the products **A1**, **B1** and **C1** in moderate yields (Method (i), entries 1-3, Table 1). Following recently reported solvent-free conditions,⁵¹ grinding 1-methyl-2-pyrrolicarboxaldehyde **2-CHO** with acetophenones **A**, **B** and **C** in the presence of NaOH with a mortar and pestle gave the corresponding products **A2**, **B2** and **C2** after only 5 min. in moderate to good yields (Method (ii), entries 4-6, Table 1). Unfortunately, attempts to apply this method to other substrates failed.

The imidazole derivatives gave variable results under these conditions and treatment with 50 mol% of BF₃.OEt₂, as described by Narender,⁵² only gave starting materials, presumably because of unproductive co-ordination to the basic nitrogen in imidazole. Use of two equivalents of BF₃.OEt₂, followed by decomplexation with NaOH, gave the desired urocanic-chalcone derivatives **A3**, **B3** and **C3** in moderate to good yields (Method (iii), entries 7-9, Table 1).

To examine the effect of the enone double bond, the dihydro-derivative **C3-H₂** was obtained in 57% yield by hydrogenation of the conjugated double bond of compound **C3** under standard conditions (entry 10, Table 1). Having obtained the core framework of the urocanic-chalcone hybrid with acetophenones **A**, **B** and **C**, further derivatives were focused on the trimethoxyaryl motif **C**. 1-Methylimidazole-2-carboxaldehyde **4-CHO** is commercially available and gave the non-natural urocanic-chalcone 1-Me derivative **C4** in the presence of BF₃.OEt₂ in 54% yield (entry 11). Methylation of the imidazole group present in **C3** using Cs₂CO₃ and MeI gave a 50:50 ratio of 1-Me **C4** and 3-Me **C5** isomers, which proved difficult to separate. Using the conditions reported for the selective methylation of the *N*-urocanic methyl ester,⁵³ NaH and MeI in DMF at 0 °C selectively gave the desired 3-Me isomer **C5** in a 75:25 ratio of **C5**:**C4** that could be separated by silica gel column chromatography (entry 12). The 2-substituted imidazole derivative **C6** was obtained using excess BF₃.OEt₂ and was methylated under standard conditions to afford compound **C7** without the formation of isomers due to the symmetry of the imidazole substituent (entries 13 and 14).

Cell Proliferation Assays

In all cases, the only stereoisomer observed was the thermodynamic *trans*-product, identified by a characteristic 3J coupling of *ca.* 15 Hz. All compounds were determined to be \geq 95% pure by HPLC and were examined for inhibition of cell proliferation *in vitro* using the MTS assay⁵⁴ with various cell lines and the results are reported as the concentration required to inhibit 50% cell proliferation (IC₅₀) (Table 1). The results are the mean of three experiments, except where indicated in Table 1, and were performed on different days with different batches of cells. Three cancer cell lines were investigated, human colon carcinoma HT29, highly metastatic human breast carcinoma MDA-MB-231 and an androgen-dependent human prostate carcinoma LNCaP. In addition, a normal primary cell line, human skin fibroblasts FEK-4, were also investigated in the MTS assay to examine selectivity.

The addition of methoxy substituents significantly increased activity of the *N*-H pyrrole derivatives (**A1-C1**) and was also observed to a lesser extent with *N*-Me pyrrole hybrids (**A2-C2**) (entries 1-3 and 4-6, Table 1). The effect of the substituents was not evident with *N*-H 4-imidazole derivatives (**A3-C3**), which showed moderate levels of activity against all three cancer cell lines, but without much selectivity (entries 7-9). The importance of the enone was demonstrated by the dramatic loss of activity of the saturated derivative **C3-H₂** (entry 10). The non-natural methylated analogue **C4** gave similar levels of activity to the unsubstituted compound **C3**, although the proposed *N*-methylurocanic trimethoxy chalcone hybrid **C5**, which has the side chain present in the sarcodictyins, did exhibit enhanced antiproliferative activity and selectivity, especially with HT29 and MDA-MB-231 (entries 11 and 12). Interestingly, the symmetrical *N*-H 2-imidazole hybrid **C6** and the methylated derivative **C7** showed similar levels of potency as hybrid **C5** against HT29 and MDA-MB-231 and displayed improved activity against LNCaP, although they are much less selective and also inhibited cell proliferation in the normal primary human skin fibroblasts FEK-4 (entries 13 and 14).

Conclusions

Combining pharmacophores present in the sarcodictyin and chalcone family of compounds, the hybrid analogue **8** was proposed and synthesised together with related isomers. It is of interest that both sarcodictyin and chalcones interact with tubulin, although they have opposing effects on microtubule assembly. From our investigations however, the lead compound is indeed hybrid chalcone **C5** which includes the *N*-methylurocanic side chain present in the sarcodictyins. It is the most active and most selective compound in the series investigated, displaying selective antiproliferative activity against HT29 and MDA-MB-231 cell lines.

It is worthy of note that the urocanic-chalcone derivative **C5** can be obtained in only two synthetic steps and displays similar levels of antiproliferative activity against HT29 as the simplified eleutherobin analogue **3** previously reported²¹ (Fig. 2 and Table 1, entry 15). Owing to their ease of synthesis, low molecular weight and promising initial results, these hybrid compounds could be used in a fragment-based lead discovery (FBLD)

approach to achieve more potent compounds.

Hybrid **C5**, together with others examined in this series, will be further investigated to determine the biological mode of action and will be reported in due course.

The simple chalcone scaffold combined with the *N*-methylurocanic ester side chain present in the sarcodictyin family of compounds has afforded biologically active hybrid analogues with the potential for improved biological activities and drug-like properties due to their ease of synthesis and the diverse range of inexpensive and commercially available starting materials.

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